one skilled in the art to make and/or use the invention. The Examiner asserts that the specification has no working examples that the administration of any agent that restores NFκB activity treats any autoimmune disease and that there is no clear guidance as to how the administration of any agents of recited in claim 43 would be administered to intracytosolically increase NFκB activity, The Examiner further states that since the specification has no working examples demonstrating that restoring NFκB activity can treat autoimmune diseases it would be unpredictable and require an undue amount of experimentation to practice Applicant's claimed invention.

Claims 41-43 and 46-48 were also rejected under 35 U.S.C. § 112 First Paragraph as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that Applicants were in possession of the claimed invention. The Examiner asserts that there is insufficient written description to show that the Applicant was in possession of any agent to treat autoimmune disease.

Claims 41-43 and 46-48 are enabled for the treatment of autoimmune disease with an agent that restores NFκB activity

Claims 41-43 and 46-48 were rejected under 35 U.S.C. § 112 First Paragraph as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to make and/or use the invention.

Applicants respectfully traverse the rejection. Applicants submit that a central premise of the Invention is that autoimmune diseases share a common etiology. There are many indicators in the art that point to autoimmune diseases being related (see below), and the current invention demonstrates unequivocally that autoimmune diseases are mechanistically linked by a deficiency in NFκB activation. Hence, Applicants submit that restoring NFκB activity can treat autoimmune diseases. Applicants submit the following pertinent observations in support of this conclusion.

Applicants submit that genetic studies on a number of autoimmune diseases including

Insulin Dependent Diabetes (IDDM), rheumatoid arthritis, multiple sclerosis and SLE have shown that approximately 15 to 30% of pairs of monozygotic twins show disease concordance compared with 5% of dizygotic twins (Harrison's Principles of Internal Medicine, 15th Edition McGraw-Hill Medical Publishing Division; www.harrisonsonline.com; Part 12, section 1, chapter 307, page 2; Exhibit A). Clustering of different autoimmune diseases in a same family is frequently observed and indicates a common genesis between different autoimmune diseases (see Familial autoimmunity and the idiopathic inflammatory myopathies by Shamim EA, Miller FW. Curr Rheumatol Rep 2000 Jun;2(3):201-11). For example, Sjögren's Syndrome (SS) often occurs in conjunction with rheumatic diseases, such as lupus and rheumatoid arthritis, of known or suspected autoimmune origins. Applicants therefore contend from the above citations that autoimmune diseases share a common genesis and that there is genetic evidence in the art which supports this assertion.

Applicants submit that genetic studies published both prior to and subsequent to the filing date of the present invention also indicate that the transcription factor NFκB is a central, indeed pivotal, component in the etiology of autoimmune diseases as disclosed in the present invention. For example, Hugot et al have demonstrated that susceptibility to Crohn's disease, a chronic inflammatory autoimmune disorder of the gastrointestinal tract, requires NOD2, a protein that activates NFκB ( Hugot et al.(2001) Nature 411, 599 – 603; Exhibit B; Ogura et al. (2001) Nature 411, 603 - 606 (2001); Exhibit C). Genetic studies by Hegazy et al also implicate NFκB in the etiology of insulin dependent diabetes (Hegazy et al. Genes Immun 2001 Oct;2(6):304-8). In addition, it is well known in the art that deficiency in NFκB/rel A, abolishes both T and B cells' immunogenic responses to an antigen (reviewed Gerondakis et al. (1999) Oncogene 18, 6888-6895; Exhibit D) and that immunogenic and autoimmune antigens elicit a series of lymphocyte-specific signaling events that ultimately converge on and activate the transcription factor, NFκB (reviewed in Goodnow, C., 2001 Lancet 357, 2115-2121; Exhibit E). Current therapeutics such as glucocorticoids, chloroquine and gold compounds that are used to treat autoimmune diseases, target and inhibit the immunogenic NFκB signalling pathway (see

Barnes, P. J. Clin. Sci. (1998) 94, 557-72; Exhibit F). One of skill in the art would therefore find no reason to not conclude from the genetic evidence, *supra*, that autoimmune diseases according to the invention are mechanistically linked and that this common mechanism involves the transcription factor NFκB. Clearly, the state of the art at the time the present application was filed, and the substantial scientific data published subsequent to Applicants filing date supports Applicants premise that autoimmune diseases are related and that this relationship revolves centrally around aberrant NFkB activity.

In the present invention, the Applicants demonstrate a role of NFκB in autoimmune diseases by studying non-obese diabetic (NOD) mice as an animal model of autoimmune disease. In addition to their propensity to develop diabetes, NOD mice exhibit spontaneous autoimmunity to the thymus, adrenal gland, salivary glands, thyroid, testis, nuclear components and red blood cells (for a review see Silveira PA. Baxter AG. Autoimmunity. 34(1): 53-64, 2001; Exhibit G). In this regard, the specification (p45, lines 12-13) also states that NOD mice are prone to "diabetes, Sjögren's syndrome and hemolytic anemia".

Applicants submit that NOD mice serve further as a model of autoimmune disease, as NOD mice present with defects of antigen presentation and T cell maturation, traits which are commonly associated with autoimmune diseases (see, for example, Kikutani and Makino 1992, *Adv. Immunol.* 51: 285; Exhibit H; Bach *C.R. Acad Sci.* 314: 45; Exhibit I). The specification states on page 47, lines 4-14:

> "Given the established role of antigen presentation in T cell education and its impairment in numerous autoimmune diseases in both humans and mice, mutations which contribute to the abnormal antigen presentation and processing in the NOD mouse (made apparent, in part, by altered class I assembly and altered presentation of syngeneic peptides) are of significant interest; therefore, the NOD mouse provides a good model system in which genetic and environmental factors influencing autoimmune diseases can be studied."

In the present invention, Applicants present numerous working examples to demonstrate that NFκB function is specifically impaired in NOD mice. The specification states:

1. "NFκBp65-associated kinase activities were strongly evident in normal mice; still no kinase activity was detected in NOD mice" (p.104, lines 9-10)

2. "Nuclear extracts from the NOD mouse do not exhibit NFκBinding activity" (page 108, lines 3-4).

3. "p50 is virtually absent from NOD mice" (page 110, line 14).

4. "TNF-α is only able to activate NFκB in the BALB/c mouse and in the Molt-4 lymphoid cell line; NOD mice do not show increased p65 activity, suggesting a disruption of normal intracellular signalling pathways of p65-mediated protection from TNF-κ stimulation" (page 112, lines 7-10).

5. "In NOD lymphocytes, however, cytosolic IkB was clearly detected after 40 minutes of stimulation and then stably expressed during TNF-α treatment. This finding indicates a likely defect in the proteasome degradation of IκBα in TNF-α-treated lymphocytes from NOD mice (Fig. l0B) (page 114, line 23 & page 115, lines 1-3).

6. "These results suggest that the activity of the proteasome particle of NOD mouse cells is impaired with regard to p105 processing" (page 121, lines 6-7).

7. "The proteasome cutting defect extended to defective p100 processing to p52 subunits as well as interrupted IκB-α degradation, indicating that NOD mouse spleen cells have an immature proteasome in which processing of p105 to the p50 subunit is blocked" (page 125, lines 14-17).

8. "This assay ....indicates defective nuclear expression of p50-p65 active forms in TNF-cc-treated NOD lymphocytes" (page 126, lines 11-12).

Applicants therefore submit that the specification and knowledge of the art teach that the NOD mouse provides an animal model for, not only, type I diabetes but autoimmune diseases in general. Applicants further contend that the molecular defect present in NOD mice is a defect in the NFκB signaling pathway and that this defect provides the molecular basis for the observed autoimmune diseases that are characteristic of NOD mice.

On page 2, section 4 of the Office Action, the Examiner indicates that "the state of the art teaches that by decreasing proteosome activity and thereby NFκB activity that one can treat a DTH response and autoimmune diseases in general." To the contrary, Applicants submit that the novelty of the present invention resides in a treatment of autoimmune diseases that requires a restoration not a reduction of NFκB activity. Applicants submit that it is the reduction in NFκB activity that contributes to defective programmed cell death and thymic T cell education which ultimately results in the survival of T cell clones that can recognize self antigens and autoimmunity. Therefore, restoration of NFκB activity, as claimed in the present invention, is predicted to restore T cell education and treat autoimmune diseases.

As shown in Declaration by Dr. Faustman, activation of NF-κB activity, using agents disclosed in the present patent application as well as those agents known in the art, effectively treats the autoimmune diseases, type I diabetes, and Sjogren's Syndrome in the NOD animal model and this can be achieved without undue experimentation.

Claims 41-43 and 46-48 are enabled for an agent that restores NFκB activity

In the Office Action, the Examiner states that "the guidance in the specification is insufficient to direct one of skill in the art to practice the full scope of the invention since there is no clear guidance as to how the administration of any agents as recited in claim 43 would be administered to intracytosolically increase NFKB activity." Applicants respectfully traverse the rejection.

Applicants submit that the teaching in the specification, combined with the knowledge in the art at the time the application was filed, would permit one of skill in the art to use the claimed invention without undue experimentation.

The specification defines the term "agent " as:

"a biochemical substance selected from the group that includes, but is not limited to, proteins, peptides or amino acids; nucleic acids such as DNA, such as full-length genes or fragments thereof derived from genomic, cDNA or artificial coding sequences, gene regulatory elements, RNA, including mRNA, tRNA, ribosomal RNA, ribozymes and antisense RNA, oligonucleotides and oligoribonucleotides, deoxyribonucleotides and ribonucleotides; carbohydrates; lipids; proteoglycans; such agents may be administered as isolated (purified) compounds or in crude mixtures, such as in a tissue, cell or cell lysate. Alternatively, "agent" may refer to an organic or inorganic chemical as is known in the art." Page 19 lines 1-8).

On page 21, lines 9-16, the specification teaches that an agent can be:

"apolipoprotein B 100, DNA repair factor TFIIH, STAT transcription factor, a mutant- or wild-type NFκB p50, a mutant- or wild-type NFκB p65, tumor necrosis factor-α, E-selectin, I-cam, and V-cam, interleukin-2, interleukin-6, a ubiquitin deconjugating enzyme (UCH), colony-stimulating factor, interferon-β, Lmp2, Lmp7, a ubiquitin-activating enzyme (El), a ubiquitin-conjugating enzyme (E2), a ubiquitin-ligase (E3), a protein kinase, a proteasome subunit and an antibody directed against one of the 240 kD and 200 kD human erythrocyte proteasome inhibitors, CF-2 and IκB."

On page 49 lines 16-18, the specification further teaches that "NFκB... is responsive to cell surface cytokines, such as tumor necrosis factor α, interleukin-l."

Applicants therefore submit that the specification teaches at least 20 "agents" that are

capable of restoring NFκB activity according to the invention.

Applicants further submit that, in the art, a plethora of proteins/ cytokines are known to activate NFκB. Pahl H.L. Oncogene (1999) 18, 6853-6866 (Exhibit J) states that over 150 different inducers of NFκB are known in the art. Specifically Pahl teaches, in Table 1: "Inducers of NFkB activity", that the following proteins, chemicals, and physical and environmental factors are all known in the art to stimulate NFkB activity.

| Condition | Reference |
|---|---|
| **Bacteria** | |
| EPEC, enterophathogenic E. coli | Savkovic et al., 1997 |
| Gardnerella vaginalis | Hashemi et al., 1999 |
| Helicobacter pylori | Mnnzenmaier et al., 1997 |
| Lactobacilli | Klebanoff et al., 1999 |
| Listeria monocytogenes | Hauf et al., 1994 |
| Micoplasma fermentans | Marie et al., 1999 |
| Mycobacteria tuberculosis | Zhang et al., 1994 |
| Neisseria gonorrhoeae | Naumann et al., 1997 |
| Rickettsia rickettsii | Sporn et al., 1997 |
| Salmonella dublin | Eaves-Pyles et al., 1999 |
| Salmonella typhimurium | Hobbie et al., 1997 |
| Shigella fexneri | Dyer et al., 199 |
| Staphyllococcus aureus | Busam et al., 1992 |
| **Bacterial Products** | |
| Diphosphoryl lipid A (Rhodobacter sphaeroides) | Lawrence et al., 1995 |
| Exotoxin B | Busam et al., 1992 |
| G(Anh) M Tetra | Dokter et al., 1994 |
| Lipoteichoic acid (Listeria) | Hauf et al., 1997 |
| Lipopolysaccharide (LPS) | Sen and Baltimore, 1986a |
| membrane lipoproteins (Micoplasma fermentans) | Garcia et al., 1998; Rawadi et al., 1999 |
| Muramyl Peptides | Schreck et al., 1992 |
| PlcA (Phospholipase) (Listeria) | Hauf et al., 1997 |
| PleB (Phospholipase) (Listeria) | Hauf et al., 1997 |
| Staphylococcus enterotoxin A and B (super antigen) | Trede et al., 1993; Busam et al., 1992 |
| Toxic Shock Syndrome Toxin 1 | Trede et al., 1993 |
| **Viruses** | |
| Adenovirus | Sharman et al., 1989 |
| Cytomegalovirus | Sambucetti et al., 1989 |
| Epstein-Barr Virus (EBV) | Hammarskj6ld and Simurda, 1992 |
| Hepatitis B Virus | Siddiqui et al., 1989 |
| Herpes Virus Saimiri | Yao et al., 1995 |
| Human Herpesvirus 6 | Ensoli et al., 1989 |
| HIV-1 | Bachelerie et al., 1991 |
| Herpex Simplex Virus -1 | Gimble et al., 1988 |
| HTLV-I | Leung and Nabel, 1988; Ballard et al., 1988 |
| Influenza Virus | Ronni et al., 1997 |
| Measles Virus | Harcourt et al., 1999 |
| Molony Marine Leukemia Virus | Pak and Faller, 1996 |
| Newcastle disease virus | Ten et al., 1993 |

| Condition | Reference |
|---|---|
| **Eukaryotic parasite** | |
| Theileria parva | Ivanov et al., 1989 |
| (Inflammatory) Cytokines | |
| IL-1 | Osborn et al., 1989 |
| IL-2 | Hazan et al., 1990 |
| IL-12 | Grohmann et al., 1998 |
| IL-15 | McDonald et al., 1998 |
| IL-17 | Shalom-Barak et al., 1998 |
| IL-18 | Matsumoto et al., 1997 |
| LIF | Grass et al., 1992 |
| THANK | Mukhopadhyay et al., 1999 |
| TNFa | Osborn et al., 1989; Israel et al., 1989a |
| TNF# | Messer et al., 1990 |
| **Physiological (Stress) Conditions** | |
| Adhesion | Lin et al., 1995b |
| Depolarization | Kaltschmidt et al., 1995 |
| Hemorrhage | Shenkar et al., Shenkar and Abraham, 1997 |
| Hyperglycemia | Yerneni et al., 1999 |
| Hyperosmotic Shock | Courtois et al., |
| Hyperoxia | Shea et al., 1996 |
| Ischemia (transient, focal) | Gabriel et al., 1999; Li et al., 1999 |
| Liver Regeneration | Tewari et al., 1992; Cressman et al., 1994 |
| Mechanical Ventilation (in vitro) | Pugin et al., 1998 |
| Reoxygenation | Rupee and Baeuerle, 1995 |
| Shear Stress | Lan et al., 1994 |
| T-cell Selection | Moore et al., 1995 |
| **Physical Stress** | |
| PPME Photosensitization | Legrand-Poels et al., 1995 |
| Ultraviolet irradiation (UV-A, B, C) | Stein et al., 1989 |
| Wounding combined with HeNe irradiation | Haas et al., 1998 |
| y Radiation | Brach et al., 1991a |
| **Oxidative Stress** | |
| Butyl Peroxide | Munroe et al., 1995 |
| Hydrogen Peroxide | Schreck et al., 1991 |
| Ozone | Haddad et al., 1996 |
| Pervanadate | Imbert et al., 1996 |
| Reoxygenation | Rupee and Baeuerle, 1995 |
| **Environmental Hazards** | |

| | |
|---|---|
| Respiratory Syncytial Virus | Mastronarde et al., 1996; Garofalo et al., 1996 |
| Rhinovirus | Zhu et al., 1996a; Zhu et al., 1996b |
| Sendai paramyxo virus | Hiscott et al., 1989 |
| Sindbis Virus | Lin et al., 1995a |
| Viral Products | |
| Adenovirus 5: EIA | Shurman et al., 1989 |
| Adenovirus: E3/19K | Pahl et al., 1996 |
| CMV: iel | Sambucetti et al., 1989 |
| Double-stranded RNA | Visvanathan and Goodbourn, 1989 |
| EBV: EBNA-2 | Scala et al., 1993 |
| EBV: LMP | Hammarskj6ld and Simurda, 1992 |
| HBV: HBx | Twu et al., 1989 |
| HBV: LHBs | Hildt et al., 1996 |
| HBV: MHBs` | Meyer et al., 1992 |
| HCV: Core protein | You et al., 1999 |
| Herpes Saimiri: HVS13 | Yao et al., 1995 |
| HIV-1: gp160 | Chirmule et al., 1994 |
| HIV-1: Tat | Westendorp et al., 1994 |
| HTLV-I: Taxl | Ballard et al., 1988; Leung and Nabel, 1988 |
| HTLV-II: Tax2 | Tanaka et al., 1996 |
| Influenza Virus: Hemagglutinin | Pahl and Baeuerle, 1995a |
| Parvovirus B19: NSI | Moffatt et al., 1996 |
| Taxol (Paclitaxel) | Hwang and Ding, 1995 |
| Vinblastine | Rosette and Karin, 1995a |
| Vincristine | Das and White, 1997 |
| *Modified Proteins* | |
| Advanced glycated end products (A | Yan *et al.*, 1994; Wautier *et al.*, 1994 |
| Amyloid Protein Fragment (fA4) | Behl *et al.*, 1994 |
| Maleylated BSA | Misra *et al.*, 1996 |
| Modified (Oxidized)LDL | Rajavashisth *et al.*, 1995; Andalibi *et al., 1993* |
| **Overexpressed Proteins (ER** | |
| CFTR | Knorre and Pahl, unpublished observation |
| Erythropoietin-Receptor | Knorre and Pahl, unpublished observation |
| Ig heavy chain | Pahl and Baeuerle, 1995b |
| MHC Class I | Pahl and Baeuerle, 1995b |
| **Receptor Ligands** | |
| Antigen (IgM-Ligand) | Marcuzzi *et al.*, 1989 |
| CDIlb/CD18-Ligand (Complement) | Thieblemont *et al.*, 1995 |
| CD28-Ligand (B7-1) | Verweij *et al.*, 1991 |
| C132-Ligand | Bressler *et al.*, 1991 |
| CD35-Ligand (Complement) | Thieblemont *et al.*, 1995 |
| C133-Ligand | Tong-Starksen *et al.*, 1989 |
| CD40-Ligand | Berberich *et al.*, 1994 |
| C134-Ligand (gpl20) | Chirmule *et al.*, 1994 |
| Fe-2a-Receptor-Ligand (IgG2a) | Muroi *et al.*, 1994 |
| Flt-l-Ligand | Reikerstorfer *et al.*, 1995 |
| Ly6A/E-Ligand | Ivanov *et al.*, 1994 |
| N-CAM | Krushel *et al.*, 1999 |
| Trail-receptor-l-Ligand (Trail) | Schneider *et al.*, 1997 |
| Trail-receptor-2-Ligand (Trail) | Schneider *et al.*, 1997 |
| Trail-receptor-4-Ligand (Trail) | Degli-Esposti *et al.*, 1997 |
| **Apoptotic Mediators** | |
| Anti-Fas/Apo-1 Trail | Rensing-Ehl *et al.*, 1995 |
| 3,3',4,4'-tetrachlorobiphenyl (PCB77) | Hennig et al., 1999 |
| Chromium | Ye et al., 1995 |
| Cigarette Smoke | Nishikawa et al., 1999 |
| Cobalt | Goebeler et al., |
| Crocidolite asbesstos fibres | Janssen et al., 1995 |
| Dicamba (herbicide, peroxisome proliferator) | Espandiari et al., 1998 |
| Lead | Ramesh et al., |
| Nickel | Goebeler et al., |
| Silica Particles | Chen et al., 1995 |
| **Therapeutically used drugs** | |
| 1-b-D-Arabinofuranosyl-cytosine (ara-C) | Strum et al., 1994 |
| Anthralin | Schmidt et al., |
| Azidothymidine (AZT) | Kurata, 1994 |
| Camptothecin | Piret and Pierre, 1996 |
| Ciprofibrate | Li et al., 1996a |
| Cisplatin | Nie et al., 1998 |
| Daunomycin | Das and White, 1997; Hellin et al., 1998 |
| Daunorubicin | Wang et al., 1996 |
| Doxorubicin | Das and White, 1997 |
| Etoposide | Bessho et al., 1994 |
| Haloperidol | Post et al., 1998 |
| Methamphetamine | Asanuma and Cadet, 1998 |
| Phenobarbital | Li et al., 1996b |
| Tamoxifen | Ferlini et al., 1999 |
| PAF (platelet activating factor) | Smith and Shearer, Mutoh *et al.*, 1994 |
| Potassium | Kaltschmidt *et al.*, 1995 |
| Thrombin | Mari *et al.*, 1994 |
| **Chemical Agents** | |
| 2-Deoxyglucose | Pahl and Baeuerle, |
| Anisomycin | Sen and Baltimore, |
| Brefeldin A | Pahl and Baeuerle, |
| Calchicine | Rosette and Karin, |
| Calcium Ionophores | Novak *et al.*, 1990 |
| Calyculin A | Suzuki *et al.*, 1994 |
| Cobalt chloride | Sultana *et al.*, 1999 |
| Con A | Rattner *et al.*, 1991 |
| Cycloheximide | Sen and Baltimore, |
| Cyclopiazonic Acid | Pahl *et al.*, 1996 |
| Forskolin | Delfino and Walker, |
| Glass fibres | Ye *et al.*, 1999 |
| Linoleic acid | Hennig *et al.*, 1996 |
| L-NMA | Peng *et al.*, 1995 |
| Lysophosphatidic acid | Shahrestanifar *et al.*, |
| Monensin | Pahl and Baeuerle unpublished |
| N-methyl-D-aspartate | Guerrini *et al.*, 1995 |
| Nocodazol | Rosette and Karin, 1995a |
| Okadaic Acid | Thevenin *et al.*, 1991 |
| PHA | Sen and Baltimore, 1986b |
| Phorbol ester | Sen and Baltimore, 1986a |
| Podophyllotoxin | Rosette and Karin, 1995a |
| Pyrogallol | Adcock *et al.*, 1994 |
| Quinolinic acid | Qin *et al.*, 1998 |
| Thapsigargin | Pahl *et al.*, 1996 |
| Tunicamycin | Pahl and Baeuerle, 1995b |
| Vinblastine | Rosette and Karin, 1995a |
| **Physiological Mediators** | |
| 12(R)-Hydroxyeicosatrienoic acid | Laniado-Schwartzman et al., 1994 |
| Amino acid analogs | Kretz-Remy et al., 1998 |

| | |
|---|---|
| | Schneider *et al.*, 1997 |
| **Mitogens, growth factors and** | |
| Bone morphogenic protein 2 | Mohan *et al.*, 1998 |
| Bone morphogenic protein 4 | Mohan *et al.*, 1998 |
| Folicle Stimulating Hormone | Delfino and Walker, 1998 |
| Human Growth Hormone | Shen *et al.*, 1997 |
| Insulin | Bertrand *et al.*, 1995 |
| M-CSF | Brach *et* al1991b |
| Nerve Growth Factor | Wood, 1995; Carter et al., 1996 |
| Platelet-Derived Growth Factor | Olashaw et al., 1992 |
| Serum | Baldwin et al., 1991 |
| TGF-a | Lee et al., 1995 |

| | |
|---|---|
| Anaphylatoxin C3a | Pan, 1998 |
| Ana h „vlatnY;n (';a | Pan 1QQR |
| Angiotensin II | Li and Brasier, 1996 |
| Basic calcium phosphate crystals | McCarthy et al., 1998 |
| Bradikinin | Pan et al., 1996 |
| C2-Ceramide (N-acetyl-sphingosine) | Andrieu et al., 1995 |
| Cerulein | Gukovsky et al., 1998; |
| Collagen lattice | xu et al., 1998 |
| Collagen Type I | Lee et al., 1995 |
| Des-ArgIO-kallidin B1 receptor | Schanstra et al., 1998 Suzuki et al., 1999 |
| f-Met-Leu-Phe | Browning et al., 1997 |
| Heat shock protein 60 (HSP 60) | Kol et al., 1999 |
| Hemoglobin | Simoni et al., 1998 |
| Hyaluronan | Noble et al., 1996 |
| Kaianic acid (Kainate) | Kaltschmidt et al., 1995 |
| Leukotriene B4 | Brach et al., 1992 |
| L-Glutamate | Guerrini et al., 1995 |
| Lysophosphatidylcholine (LysoPC) | Zhu et al., 1997 |

Applicants submit that the specification teaches a number of agents that restore NFκB activity and that the cited agents are indeed representative of the agents known in the art. From the specification and knowledge of the art, Applicants submit that a person of skill in the art would therefore know how to perform the claimed method comprising an "agent that restores NFκB activity".

The Examiner asserts that the specification is insufficient to direct one of skill in the art to practice the full scope of the invention and that it would be unpredictable and require an undue amount of experimentation to practice the claimed invention.

Applicants submit that amount of experimentation required to practice the invention is not undue. As stated in the MPEP at § 2164.01(a):

> There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to:
>
> (A) The breadth of the claims;
>
> (B) The nature of the invention;
>
> (C) The state of the prior art;

> (D) The level of one of ordinary skill;
> (E) The level of predictability in the art;
> (F) The amount of direction provided by the inventor;
> (G) The existence of working examples; and
> (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

(citing *In re Wands*, 858 F.2d 731, 737, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988)). In the *Wands* case, the MPEP notes that:

> The Court held that the specification was enabling with respect to the claims at issue and found that "there was considerable direction and guidance" in the specification; there was "a high level of skill in the art at the time the application was filed;" and "all of the methods needed to practice the invention were well known." 858 F.2d at 740, 8 USPQ2d at 1406. After considering all the factors related to the enablement issue, the court concluded that "it would not require undue experimentation to obtain antibodies needed to practice the claimed invention." *Id.*, 8 U.S.P.Q.2d at 1407.

Applicants respectfully submit that the Examiner is only focusing on some of the factors noted above, while ignoring others. For example, Applicants submit that the Examiner is focusing on the breadth of the claims and the existence of working examples, rather than on the fact the state of the prior art with respect to agents which activate NFkB, and autoimmune disease is mature, that there is a high level of skill possessed by one in the art, and that the specification provides adequate direction to make and use the present invention.

Applicants submit that the claims are not overly broad. The teachings of the specification, combined with the state of the art relating to agents which activate NFκB activity, results in a generally high level of skill in the field, and the predictability in the art, with respect to which agents could reasonably be expected by one of skill in the art to restore NFκB activity, is substantial. Applicants submit that the field of NFκB activation and cellular signaling is one

in which experimentation is considered normal. Applicants have taught specifically in the specification over 20 "agents" useful for restoration of NFκB activity, noting both specific agents such as apolipoprotein B 100, and general agents such as cell surface cytokines.

Applicants submit that the level of one of skill in the art is high. Applicants submit that the field of NFkB activation and autoimmune disease research is mature, with over 200,000 literature references published (MEDLINE database) relating to autoimmune disease, and as noted above, over 150 known agents which are capable of restoring NFkB activity.

With respect to the predictability in the art, Applicants submit that, provided with the teachings in the present application coupled with the state of the art, one of ordinary skill in the art would not be required to perform undue, or unpredictable experimentation to carry out the claimed invention. The Examiner asserts that since the teachings of the present invention relate to a method of treating autoimmune disease (increasing NFkB activity) which runs countercurrent with the general strategy for autoimmune disease treatment in the art (decreasing NFkB activity), that the present invention is unpredictable. Applicants submit that it is this very divergence from standard therapies which make the present invention novel and unobvious. Applicants respectfully submit that the if the predictability of an invention for purposes of meeting the enablement requirement was predicated upon the invention modeling itself after the prior art, then no patent would ever issue, as no invention would be novel. Applicants submit that as noted above in *In re Wands*, there is "considerable direction and guidance" provided in the present specification to enable one to practice the claimed invention, there was "a high level of skill in the art at the time the application was filed", and that "all the methods needed to practice the invention were well known".

Applicants thus submit that given the knowledge and maturity in the art, it is neither cumbersome nor costly to test the specific agents taught or specific agents encompasses by the broad classes of agents for use in the invention. Time and expense are merely factors in the consideration of undue experimentation, and they are not controlling factors (*United States v.*

*Telectronics Inc.*, 857 F.2d 778, 785, 8 U.S.P.Q. 2d 1217, 1223 (Fed. Cir. 1988), *cert. denied*, 490 U.S. 1046 (1998). In *In re Wands*, the court stated that "[e]nablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. 'The key word is 'undue' not 'experimentation' '" (citing *In re Angstadt*, 537 F. 2d 498 at 504, 190 U.S.P.Q. 214 at 219 (C.C.P.A. 1976)). The Court also stated that "the test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." (citing *In re Jackson*, 217 U.S.P.Q. 804 at 807 (Bd. App. 1982)). In addition, the Federal Circuit has held that claims may encompass some inoperative species, so long as the number of inoperative species does not become significant and force one of ordinary skill into undue experimentation in order to practice the invention (*Atlas Powder Co. v. E.I. du Pont de Nemours & Co.*, 750 F.2d 1569, 224 U.S.P.Q. 409 (Fed. Cir. 1984)). Furthermore, it is clear and well established in the law that the specification does not need to re-teach what is already known in the art. Accordingly, Applicants submit that the claims of the present invention, given the teachings in the specification and the general knowledge in the art, are enabled for an "agent which restores NFκB activity", and that it would not require undue experimentation to obtain agents needed to practice the claimed invention.

In conclusion, Applicants submit that the state of the art clearly indicates that autoimmune diseases are related in their etiology, and that the present invention combined with the declaration of Dr. Faustman, submitted herewith, establishes that the restoration of NFκB activity is successful in treating the autoimmune disease, type I diabetes in the NOD mouse model. Applicants submit that, given the knowledge in the art of the relatedness of autoimmune diseases, the specific teachings provided in the specification as filed, and the declaration of Dr. Faustman, one of skill in the art would be able, with routine experimentation, to extrapolate the present teachings to treat the genus of autoimmune diseases as claimed. Applicants therefore submit that the specification enables a person skilled in the art to make and use an agent of the

invention. Applicants further submit that the specification enables a method for the restoration of NFκB activity wherein administering an agent of the invention restores NFκB activity and treats autoimmune disease, and that one of ordinary skill in the art would be able to perform the invention, as claimed, without undue experimentation. Applicants therefore respectfully request reconsideration and withdrawal of the rejection.

Rejection of Claims 41-43 and 46-48 Under 35 U.S.C. § 112 First Paragraph

Claims 41-43 and 46-48 were rejected under 35 U.S.C. § 112 First Paragraph as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that Applicants were in possession of the claimed invention. The Examiner asserts that there is insufficient written description to show that the Applicant was in possession of any agent to treat autoimmune disease. The Examiner states that the term "agent" would include an essentially unlimited number of undefined compounds with no common structural features. The Examiner further states one of skill in the art would therefore conclude that the specification fails to disclose a representative number of species to describe the claimed genus.

Applicants respectfully traverse the rejection. The Examiner is asserting that Applicants have not disclosed a representative number of species by disclosure of relevant identifying characteristics such as functional characteristics coupled with a known or disclosed correlation between structure and function. Applicants acknowledge that the specification does not disclose common structural attributes of "agents" useful for restoring NFkB activity according to the invention. Applicants respectfully remind the Examiner, however, that the claims of the present invention are not directed to an "agent" but to a method relating to a newly recognized effect of a class of agents, all of which restore NFkB activity. That is, "agents" according to the present invention are all related functionally. Applicants submit that it is well settled law that for a known class of compounds (i.e., agents which restore NFkB activity), a disclosure of a functional relationship between the members of the class can be sufficient to meet the written description

requirement. As stated in the MPEP, the board of appeals held in *In re Herschler* that disclosure of corticosteroid in DMSO is sufficient to support claims drawn to a method of using a mixture of a "physiologically active steroid" and DMSO because "use of known chemical compounds in a manner auxiliary to the invention must have a corresponding written description only so specific as to lead one having ordinary skill in the art to that class of compounds. Furthermore, the board held that "a functional recitation of those known compounds in the specification may be sufficient as that description". Applicants submit that the class of "agents which restore NFkB activity" was known to those of skill in the art at the time the present application was filed (see below), and thus the burden of the written description requirement is such that the specification must contain sufficient teachings to "lead one having ordinary skill in the art to that class of compounds". Applicants submit that the disclosure of the present application coupled with the state of the art relating to activation of NFkB, would have reasonably lead one of skill in the art to the class of agents which are capable of activating NFkB.

Applicants submit that the specification of the present invention teaches a representative number of "agents" that can restore NFκB activity. Specifically, the specification states:

The specification defines the term "agent " as:

"a biochemical substance selected from the group that includes, but is not limited to, proteins, peptides or amino acids; nucleic acids such as DNA, such as full-length genes or fragments thereof derived from genomic, cDNA or artificial coding sequences, gene regulatory elements, RNA, including mRNA, tRNA, ribosomal RNA, ribozymes and antisense RNA, oligonucleotides and oligoribonucleotides, deoxyribonucleotides and ribonucleotides; carbohydrates; lipids; proteoglycans; such agents may be administered as isolated (purified) compounds or in crude mixtures, such as in a tissue, cell or cell lysate. Alternatively, "agent" may refer to an organic or inorganic chemical as is known in the art." Page 19 lines 1-8).

On page 21, lines 9-16, the specification teaches an agent can be:

"apolipoprotein B 100, DNA repair factor TFIIH, STAT transcription factor, a mutant- or wild-type NFκB p50, a mutant- or wild-type NFκB p65, tumor necrosis factor-α, E-selectin, I-cam, and V-cam, interleukin-2, interleukin-6, a ubiquitin deconjugating enzyme (UCH), colony-stimulating factor, interferon-β, Lmp2, Lmp7, a ubiquitin-activating enzyme (El), a ubiquitin-conjugating enzyme (E2), a ubiquitin-ligase (E3), a protein kinase, a proteasome subunit and an antibody directed against one of the 240 kD and 200 kD human erythrocyte proteasome inhibitors, CF-2 and IκB."

In addition the specification teaches that:

"NFκB... is responsive to cell surface cytokines, such as tumor necrosis factor α, interleukin-l and cytoplasmic activation of this factor is required prior to nuclear localization" (page 49, lines 16-18).

"Cell surface signals on lymphocytes activate NFκB through cascades of kinases (Verma et al., 1995, supra; Baeuerle and Baltimore, 1996, Cell, 87: 13-20)" (page 50, lines 18-19).

"When ubiquitinated IκB is degraded by the proteasome, NFκB translocates to the nucleus where it activates transcription. As is stated in Hopkin (1997, supra), the combination of two highly specific processes, phosphorylation and ubiquitination, has been utilized by cells to control complex signal-transduction pathways precisely. " (page 50, lines 11-14)

Applicants therefore submit that the specification teaches at least 20 "agents" that are capable of restoring NFκB activity according to the invention.

Applicants further submit that a plethora of factors/ cytokines are known to activate NFκB. Pahl H.L. Oncogene (1999) 18, 6853-6866 (Exhibit J) states that over 150 different inducers of NFkappaB are known in the art and include:

| Condition | Reference |
|---|---|
| **Bacteria** | |
| EPEC, enterophathogenic E. coli | Savkovic et al., 1997 |
| Gardnerella vaginalis | Hashemi et al., 1999 |
| Helicobacter pylori | Mnnzenmaier et al., 1997 |
| Lactobacilli | Klebanoff et al., 1999 |
| Listeria monocytogenes | Hauf et al., 1994 |
| Micoplasma fermentans | Marie et al., 1999 |
| Mycobacteria tuberculosis | Zhang et al., 1994 |
| Neisseria gonorrhoeae | Naumann et al., 1997 |
| Rickettsia rickettsii | Sporn et al., 1997 |
| Salmonella dublin | Eaves-Pyles et al., 1999 |
| Salmonella typhimurium | Hobbie et al., 1997 |
| Shigella fexneri | Dyer et al., 199 |
| Staphyllococcus aureus | Busam et al., 1992 |
| **Bacterial Products** | |
| Diphosphoryl lipid A (Rhodobacter sphaeroides) | Lawrence et al., 1995 |
| Exotoxin B | Busam et al., 1992 |
| G(Anh) M Tetra | Dokter et al., 1994 |
| Lipoteichoic acid (Listeria) | Hauf et al., 1997 |
| Lipopolysaccharide (LPS) | Sen and Baltimore, 1986a |
| membrane lipoproteins (Micoplasma fermentans) | Garcia et al., 1998; Rawadi et al., 1999 |
| Muramyl Peptides | Schreck et al., 1992 |
| P1cA (Phospholipase) (Listeria) | Hauf et al., 1997 |
| P1eB (Phospholipase) (Listeria) | Hauf et al., 1997 |
| Staphylococcus enterotoxin A and B (super antigen) | Trede et al., 1993; Busam et al., 1992 |
| Toxic Shock Syndrome Toxin 1 | Trede et al., 1993 |
| **Viruses** | |
| Adenovirus | Sharman et al., 1989 |
| Cytomegalovirus | Sambucetti et al., 1989 |
| Epstein-Barr Virus (EBV) | Hammarskj6ld and Simurda, 1992 |
| Hepatitis B Virus | Siddiqui et al., 1989 |
| Herpes Virus Saimiri | Yao et al., 1995 |
| Human Herpesvirus 6 | Ensoli et al., 1989 |
| HIV-1 | Bachelerie et al., 1991 |
| Herpex Simplex Virus -1 | Gimble et al., 1988 |
| HTLV-I | Leung and Nabel, 1988; Ballard et al., 1988 |
| Influenza Virus | Ronni et al., 1997 |
| Measles Virus | Harcourt et al., 1999 |
| Molony Marine Leukemia Virus | Pak and Faller, 1996 |
| Newcastle disease virus | Ten et al., 1993 |
| Respiratory Syncytial Virus | Mastronarde et al., 1996; Garofalo et al., 1996 |
| Rhinovirus | Zhu et al., 1996a; Zhu et al., 1996b |
| Sendai paramyxo virus | Hiscott et al., 1989 |
| Sindbis Virus | Lin et al., 1995a |
| Viral Products | |
| Adenovirus 5: EIA | Shurman et al., 1989 |
| Adenovirus: E3/19K | Pahl et al., 1996 |

| Condition | Reference |
|---|---|
| **Eukaryotic parasite** | |
| Theileria parva | Ivanov et al., 1989 |
| (Inflammatory) Cytokines | |
| IL-1 | Osborn et al., 1989 |
| IL-2 | Hazan et al., 1990 |
| IL-12 | Grohmann et al., 1998 |
| IL-15 | McDonald et al., 1998 |
| IL-17 | Shalom-Barak et al., 1998 |
| IL-18 | Matsumoto et al., 1997 |
| LIF | Grass et al., 1992 |
| THANK | Mukhopadhyay et al., 1999 |
| TNFa | Osborn et al., 1989; Israel et al., 1989a |
| TNF# | Messer et al., 1990 |
| **Physiological (Stress) Conditions** | |
| Adhesion | Lin et al., 1995b |
| Depolarization | Kaltschmidt et al., 1995 |
| Hemorrhage | Shenkar et al., Shenkar and Abraham, 1997 |
| Hyperglycemia | Yerneni et al., 1999 |
| Hyperosmotic Shock | Courtois et al., |
| Hyperoxia | Shea et al., 1996 |
| Ischemia (transient, focal) | Gabriel et al., 1999; Li et al., 1999 |
| Liver Regeneration | Tewari et al., 1992; Cressman et al., 1994 |
| Mechanical Ventilation (in vitro) | Pugin et al., 1998 |
| Reoxygenation | Rupee and Baeuerle, 1995 |
| Shear Stress | Lan et al., 1994 |
| T-cell Selection | Moore et al., 1995 |
| **Physical Stress** | |
| PPME Photosensitization | Legrand-Poels et al., 1995 |
| Ultraviolet irradiation (UV-A, B, C) | Stein et al., 1989 |
| Wounding combined with HeNe irradiation | Haas et al., 1998 |
| y Radiation | Brach et al., 1991a |
| **Oxidative Stress** | |
| Butyl Peroxide | Munroe et al., 1995 |
| Hydrogen Peroxide | Schreck et al., 1991 |
| Ozone | Haddad et al., 1996 |
| Pervanadate | Imbert et al., 1996 |
| Reoxygenation | Rupee and Baeuerle, 1995 |
| **Environmental Hazards** | |
| 3,3',4,4'-tetrachlorobiphenyl (PCB77) | Hennig et al., 1999 |
| Chromium | Ye et al., 1995 |
| Cigarette Smoke | Nishikawa et al., 1999 |
| Cobalt | Goebeler et al., |
| Crocidolite asbesstos fibres | Janssen et al., 1995 |
| Dicamba (herbicide, peroxisome proliferator) | Espandiari et al., 1998 |
| Lead | Ramesh et al., |
| Nickel | Goebeler et al., |

| | |
|---|---|
| CMV: iel | Sambucetti et al., 1989 |
| Double-stranded RNA | Visvanathan and Goodbourn, 1989 |
| EBV: EBNA-2 | Scala et al., 1993 |
| EBV: LMP | Hammarskj6ld and Simurda, 1992 |
| HBV: HBx | Twu et al., 1989 |
| HBV: LHBs | Hildt et al., 1996 |
| HBV: MHBs' | Meyer et al., 1992 |
| HCV: Core protein | You et al., 1999 |
| Herpes Saimiri: HVS13 | Yao et al., 1995 |
| HIV-1: gp160 | Chirmule et al., 1994 |
| HIV-1: Tat | Westendorp et al., 1994 |
| HTLV-I: Taxl | Ballard et al., 1988; Leung and Nabel, 1988 |
| HTLV-II: Tax2 | Tanaka et al., 1996 |
| Influenza Virus: Hemagglutinin | Pahl and Baeuerle, 1995a |
| Parvovirus B19: NSI | Moffatt et al., 1996 |
| Taxol (Paclitaxel) | Hwang and Ding, 1995 |
| Vinblastine | Rosette and Karin, 1995a |
| Vincristine | Das and White, 1997 |
| *Modified Proteins* | |
| Advanced glycated end products (A | Yan *et al.*, 1994; Wautier *et al.*, 1994 |
| Amyloid Protein Fragment (fA4) | Behl *et al.*, 1994 |
| Maleylated BSA | Misra *et al.*, 1996 |
| Modified (Oxidized)LDL | Rajavashisth *et al.*, 1995; Andalibi *et al., 1993* |
| **Overexpressed Proteins (ER** | |
| CFTR | Knorre and Pahl, unpublished observation |
| Erythropoietin-Receptor | Knorre and Pahl, unpublished observation |
| Ig heavy chain | Pahl and Baeuerle, 1995b |
| MHC Class I | Pahl and Baeuerle, 1995b |
| **Receptor Ligands** | |
| Antigen (IgM-Ligand) | Marcuzzi *et al.*, 1989 |
| CDllb/CD18-Ligand (Complement) | Thieblemont *et al.*, 1995 |
| CD28-Ligand (B7-1) | Verweij *et al.*, 1991 |
| C132-Ligand | Bressler *et al.*, 1991 |
| CD35-Ligand (Complement) | Thieblemont *et al.*, 1995 |
| C133-Ligand | Tong-Starksen *et al.*, 1989 |
| CD40-Ligand | Berberich *et al.*, 1994 |
| C134-Ligand (gpl20) | Chirmule *et al.*, 1994 |
| Fe-2a-Receptor-Ligand (IgG2a) | Muroi *et al.*, 1994 |
| Flt-l-Ligand | Reikerstorfer *et al.*, 1995 |
| Ly6A/E-Ligand | Ivanov *et al.*, 1994 |
| N-CAM | Krushel *et al.*, 1999 |
| Trail-receptor-l-Ligand (Trail) | Schneider *et al.*, 1997 |
| Trail-receptor-2-Ligand (Trail) | Schneider *et al.*, 1997 |
| Trail-receptor-4-Ligand (Trail) | Degli-Esposti *et al.*, 1997 |
| **Apoptotic Mediators** | |
| Anti-Fas/Apo-1 Trail | Rensing-Ehl *et al.*, 1995; Schneider *et al.*, 1997 |
| **Mitogens, growth factors and** | |
| Bone morphogenic protein 2 | Mohan *et al.*, 1998 |
| Bone morphogenic protein 4 | Mohan *et al.*, 1998 |
| Folicle Stimulating Hormone | Delfino and Walker, 1998 |
| Human Growth Hormone | Shen *et al.*, 1997 |
| Insulin | Bertrand *et al.*, 1995 |
| Silica Particles | Chen et al., 1995 |
| **Therapeutically used drugs** | |
| 1-b-D-Arabinofuranosyl-cytosine (ara-C) | Strum et al., 1994 |
| Anthralin | Schmidt et al., |
| Azidothymidine (AZT) | Kurata, 1994 |
| Camptothecin | Piret and Pierre, 1996 |
| Ciprofibrate | Li et al., 1996a |
| Cisplatin | Nie et al., 1998 |
| Daunomycin | Das and White, 1997; Hellin et al., 1998 |
| Daunorubicin | Wang et al., 1996 |
| Doxorubicin | Das and White, 1997 |
| Etoposide | Bessho et al., 1994 |
| Haloperidol | Post et al., 1998 |
| Methamphetamine | Asanuma and Cadet, 1998 |
| Phenobarbital | Li et al., 1996b |
| Tamoxifen | Ferlini et al., 1999 |
| PAF (platelet activating factor) | Smith and Shearer, Mutoh *et al.*, 1994 |
| Potassium | Kaltschmidt *et al.*, 1995 |
| Thrombin | Mari *et al.*, 1994 |
| **Chemical Agents** | |
| 2-Deoxyglucose | Pahl and Baeuerle, |
| Anisomycin | Sen and Baltimore, |
| Brefeldin A | Pahl and Baeuerle, |
| Calchicine | Rosette and Karin, |
| Calcium Ionophores | Novak *et al.*, 1990 |
| Calyculin A | Suzuki *et al.*, 1994 |
| Cobalt chloride | Sultana *et al.*, 1999 |
| Con A | Rattner *et al.*, 1991 |
| Cycloheximide | Sen and Baltimore, |
| Cyclopiazonic Acid | Pahl *et al.*, 1996 |
| Forskolin | Delfino and Walker, |
| Glass fibres | Ye *et al.*, 1999 |
| Linoleic acid | Hennig *et al.*, 1996 |
| L-NMA | Peng *et al.*, 1995 |
| Lysophosphatidic acid | Shahrestanifar *et al.*, |
| Monensin | Pahl and Baeuerle unpublished |
| N-methyl-D-aspartate | Guerrini *et al.*, 1995 |
| Nocodazol | Rosette and Karin, 1995a |
| Okadaic Acid | Thevenin *et al.*, 1991 |
| PHA | Sen and Baltimore, 1986b |
| Phorbol ester | Sen and Baltimore, 1986a |
| Podophyllotoxin | Rosette and Karin, 1995a |
| Pyrogallol | Adcock *et al.*, 1994 |
| Quinolinic acid | Qin *et al.*, 1998 |
| Thapsigargin | Pahl *et al.*, 1996 |
| Tunicamycin | Pahl and Baeuerle, 1995b |
| Vinblastine | Rosette and Karin, 1995a |
| **Physiological Mediators** | |
| 12(R)-Hydroxyeicosatrienoic acid | Laniado-Schwartzman et al., 1994 |
| Amino acid analogs | Kretz-Remy et al., 1998 |
| Anaphylatoxin C3a | Pan, 1998 |
| Ana h „vlatnY;n (';a | Pan 1QQR |
| Angiotensin II | Li and Brasier, 1996 |
| Basic calcium phosphate crystals | McCarthy et al., 1998 |
| Bradikinin | Pan et al., 1996 |
| C2-Ceramide (N-acetyl-sphingosine) | Andrieu et al., 1995 |
| Cerulein | Gukovsky et al., 1998; |
| Collagen lattice | xu et al., 1998 |

| | | | |
|---|---|---|---|
| M-CSF | Brach *et* al1991b | Collagen Type I | Lee et al., 1995 |
| Nerve Growth Factor | Wood, 1995; Carter et al., 1996 | Des-ArgIO-kallidin B1 receptor | Schanstra et al., 1998 Suzuki et al., 1999 |
| Platelet-Derived Growth Factor | Olashaw et al., 1992 | f-Met-Leu-Phe | Browning et al., 1997 |
| Serum | Baldwin et al., 1991 | Heat shock protein 60 (HSP 60) | Kol et al., 1999 |
| TGF-a | Lee et al., 1995 | Hemoglobin | Simoni et al., 1998 |
| | | Hyaluronan | Noble et al., 1996 |
| | | Kaianic acid (Kainate) | Kaltschmidt et al., 1995 |
| | | Leukotriene B4 | Brach et al., 1992 |
| | | L-Glutamate | Guerrini et al., 1995 |
| | | Lysophosphatidylcholine (LysoPC) | Zhu et al., 1997 |

The Applicants submit therefore, that the at least 20 agents taught in the specification together with the over 150 agents known to induce NFκB in the art would clearly indicate to one of skill in the art that the Applicants were in possession of "an agent that restores NFκB activity". Applicants further submit the MPEP (2163) clearly sets forth that the written description requirements state that "what constitutes a representative number [of species] is an inverse function of the skill and knowledge in the art... a representative number of species does not require the description to be of such specificity that it would provide individual support for each species the genus embraces".

Applicants submit that the skill and knowledge in the art relating to NFκB activation is high, as more than 150 agents, which can restore NFκB activity, were known around the time that the present application was filed. Accordingly, the at least 20 agents that restore NFκB activity taught in the specification, in view of what was known in the art at the time of filing, constitute a representative number of species. One of skill in the art would have reasonably concluded that Applicants were in possession of the invention at the time of filing. If the Examiner maintains this rejection, Applicants respectfully request that the Examiner provide the reasoning why, given the breadth of knowledge in the art relating to NFκB activation, one of skill in the art would doubt Applicants were in possession of an agent which restores NFκB activity. Applicants respectfully request withdrawal of the rejection.

## CONCLUSION

Applicants submit that all claims are allowable as written and respectfully request early favorable action by the Examiner. If the Examiner believes that a telephone conversation with Applicants' attorney would expedite prosecution of this application, the Examiner is cordially invited to call the undersigned attorney of record.

Respectfully submitted, Matthew Beaudet 50,649; Signing For:

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